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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,795	09/05/2001	Gunther Berndl	49727	4232

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EXAMINER
GOLLAMUDI, SHARMILA S

ART UNIT	PAPER NUMBER
1616	13

DATE MAILED: 06/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/914,795	Applicant(s) BERNDL ET AL.	
	Examiner Sharmila S. Gollamudi	Art Unit 1616	

-- The MAILING DATE of this communicati n appears on the cover sheet with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt of Extension of Time and Amendment D received on March 31, 2003 is acknowledged. Claims 1-6 are pending in this application.

Response to Arguments

Applicant's arguments with respect to claims 1-6 have been considered but are moot in view of the new ground(s) of rejection in light of Amendment D.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baert et al (6,365,188) in view of Klimesch et al (4,880,585).

Baert et al teach a solid mixture of cyclodextrin prepared via melt extrusion. A tablet containing cyclodextrin (67%), an active (33%), and crospovidone (5%-20%), colloidal silicon dioxide (0.4%-0. 5%), and sterotex (0.9%-1%) is taught. Table 1 and

examples. Note that all percentages are approximations and the active is calculated based on preferred ratio of 1:3. The reference teaches various ratios of the active to cyclodextrin. See Table 1. Further, a temperature of 239 degrees Celsius is exemplified but Baert discloses that different temperatures may be applied and discloses the method of ascertaining the required temperature. See column 5, lines 1-12. The melt-extruded mixture is preferably prepared without water or a solvent. See column 4, lines 64-68. The process involves mixing one or more cyclodextrins with the active and additives, then melting the mixture until all components are melted, extruding the mixture, and cooling. See column 4. The extrusion process requires thermomelting or thermoplastic polymers. The extruder has counterotating screw with different shapes. See column 5.

Although Baert teaches thermoplastic polymers in general but does not teach the instant polymers.

Klimesch et al teaches a method of continuous tableting using a molding calendar with opposite rollers (col. 1, lines 16-27). The reference teaches the use of instant polymeric binder and instant temperature (col. 2, lines 40-68). The reference teaches the preferable temperature is 60-130 degrees Celsius to be extrudable but the components of the mixture and polymer should melt. Kilmesch teaches that the instant polymers are pharmacologically acceptable and convert the pharmacological actives into paste to be extruded. The advantage of the process is it makes premixing unnecessary (col. 1, lines 28-34).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Baert et al and Kilmesch et al and incorporate the instant polymers into Baert's process. One would be motivated to do so since Kilmesch teaches that the instant polymers are pharmaceutically acceptable and conventionally utilized in extrusion processes to make the composition into a paste. Furthermore, a skilled artisan would expect similar results since Baert teaches a melt extrusion process that requires thermoplastic polymers such as those taught in Kilmesch.

Furthermore, it is deemed obvious to manipulate the temperate parameters of WO since not only does WO provide the guidance to determine the optimal range, Kilmesch teaches that the temperature depends on the melting point of all the components in the mixture. Therefore, one would be motivated to manipulate the temperature accordingly based on the components and their physical properties.

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baert et al (6,365,188) in view of Schultz et al (6,194,395) or vice-versa, optionally in further view of Baert et al (6,342,245).

Baert et al teach a solid mixture of cyclodextrin prepared via melt extrusion. A tablet containing cyclodextrin (67%), an active (33%), and crospovidone (5%-20%), colloidal silicon dioxide (0.4%-0. 5%), and sterotex (0.9%-1%) is taught. Table 1 and examples. Note that all percentages are approximations and the active is calculated based on preferred ratio of 1:3. The reference teaches various ratios of the active to cyclodextrin. See Table 1. Further, Baert discloses that different temperatures may be

applied and discloses the method of ascertaining the required temperature. See column 5, lines 1-12. The melt-extruded mixture is preferably prepared without water or a solvent. See column 4, lines 64-68. The process involves mixing one or more cyclodextrins with the active and additives, then melting the mixture until all components are melted, extruding the mixture, and cooling. See column 4. The extrusion process requires thermomelting or thermoplastic polymers. The extruder has counterotating screw with different shapes. See column 5.

Although Baert et al teach crospovidone as a binder, Baert does not specify other binders that may be used such as instant binders.

Schultz et al teach cyclodextrin cladribine formulations. Column 3 teaches instant cyclodextrin derivatives. The solid dosage form contains 1-15 mg cladribine, 100-500 mg cyclodextrin, 100-300 mg microcrystalline cellulose, 10-200 mg crospovidone, 1-5 mg colloidal silicon dioxide, and 2-10 mg sterotex. Note example. Other binders that may be used are carboxymethylcellulose, croscarmellose, and PVP. The reference discloses that WO 97/18839 teaches the suitable process of extrusion. Note column 5, lines 50-65.

Baert et al teach the specifics of the melt extrusion process wherein the components are mixed optionally with additives, heated, kneaded, and extruded. Baert et al teach that one of the most important parameters of melt-extrusion is temperature and operating temperatures can range from 120-300 degrees Celsius. A preferable range is 170-230 degrees Celsius, and particularly between 180-220 degrees Celsius. Baert et al disclose that the temperature is dependent on melting the active into the

polymer to obtain high bioavailability and too high temperatures cause the polymer to decompose. See column 8, lines 8-25.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of WO and Schultz and substitute WO's crospovidone with PVP to arrive at instant invention. One would be motivated to do so since Schultz teaches the equivalence of crospovidone, MC, and PVP as binders; therefore it would have been obvious to obtain similar results from the substitution since the components are functionally equivalent.

Furthermore, it is deemed obvious to manipulate the temperate parameters of WO since not only does WO provide the guidance to determine the optimal range, Schultz et al teach that the temperature depends on the melting point of all the components in the mixture. Therefore, one would be motivated to manipulate the temperature accordingly based on the components and their physical properties.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharmila S. Gollamudi whose telephone number is (703) 305-2147. The examiner can normally be reached on M-F (7:30-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jose Dees can be reached on (703) 308-4628. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

SSG
June 5, 2003

MICHAEL G. HARTLEY
PRIMARY EXAMINER